

July 1, 2021

Editor-in-Chief
World Journal of Clinical Cases

Re: Revised version of manuscript No. 63101

Dear Editor:

Please find enclosed our revised paper entitled " Atypical granular cell tumor of the urinary bladder: a case report and review of the literature " (No. 63101). We have revised the manuscript based on the reviewers' comments and suggestions with all changes underlined. We thank you, the editor and reviewers for your constructive comments, and hope that our substantial revisions have resulted in a manuscript that is now satisfactory for publication in *World Journal of Clinical Cases*.

The following are point-by-point replies to the editor's and reviewers' concerns regarding our submitted paper revision. The reviewers' comments are colored in blue; our responses are colored in black, and changes made to the manuscript are colored in red.

Round-2

Reviewer #1:

The authors have answered accordingly to the reviewer comments

Response: We are deeply thankful to the reviewer's comment, hoping that our re-revision manuscript could meet the requirements of our conditional acceptance.

Reviewer #2:

The presentation of the article can be improved. Kindly refer to the previously published case reports to get acclimatized to the language used in scientific papers.

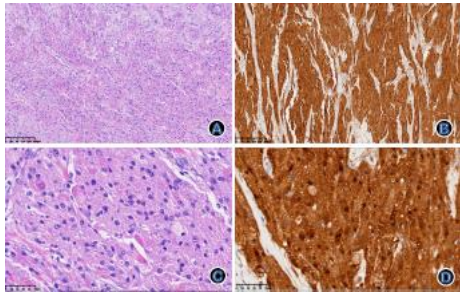
Response: Thank you for the reviewer's suggestion. We've already re-edit the language of the paper to make it more scientific and professional.

Round-1

Reviewer #3:

Figures 2 and 3: In the legend, specify what is indicated by the arrows. Figure 4: give the magnification with a scale bar on images A and B.

Response: We appreciate the reviewer's comment. We've specified the arrows in Figures 2 and 3 to make the legends more clear to understand (Page 16 Line 380-381, Page 17 Line 385-387). And we also added the scale bar on Figure 5A、5B、5C、5D as follows.



Reviewer #4:

1. There are no operative figures showing partial cystectomy.

Response:

Thanks for the reviewer's suggestion which is indeed more specific and useful. We've already added the operative figures to make the surgical options of laparoscopic partial cystectomy more provable. (Page 17)

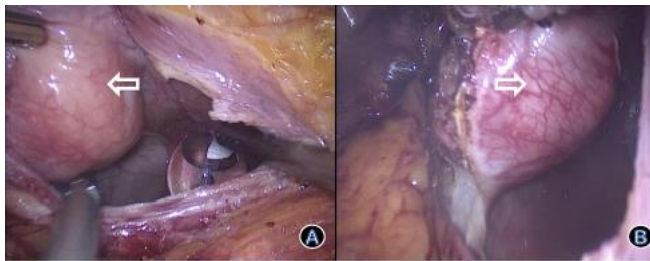


Figure 4 Operative figures of laparoscopic partial cystectomy: The round solid neoplasm of bladder was resected under laparoscopy assisted (white arrows).

2. While doing laparoscopic partial cystectomy, why lymph nodes were not removed as per protocol when lesion was involving muscle on preoperative imaging.

Response:

The reviewer's comment is valuable. Depending on report of frozen-specimen during operation, the tumor is mesenchymal neurogenic or myogenic tumor with negative margins. Combining with leiomyoma of preoperative diagnosis, we took partial cystectomy as the more conservative surgical option consequently despite the lesion was involving the muscular layer, which improved the survival quality for the patient.

3. There is disparity in reporting about lymph nodes on PET Scan and Ct scan postoperatively.

Response:

We are deeply thankful to the reviewer for raising this important point. Although the lymph nodes enlargement was detected by PET Scan three weeks after operation, the further CT Scan performed every three months during routine follow-up revealed that there is no recurrence or apparent lymph node enlargement of retroperitoneal and

bilateral iliac vascular region. In view of the above, we attribute the disparity reports about lymph nodes on PET Scan and Ct scan to the irritable inflammatory reaction, and we have specified this description on the manuscript as follows.

During a follow-up period of 6 months, no evidence of recurrence or lymph node enlargement was detected. (Page 8, Line 161-163)

Furthermore, the lymph nodes enlargement of retroperitoneal and bilateral iliac vascular region was detected by PET Scan three weeks after operation, nevertheless, the further CT Scan during routine follow-up revealed that there is no recurrence or apparent lymph node enlargement. In view of the above, we attribute the disparity reports about lymph nodes on PET Scan and Ct scan to the irritable inflammatory reaction. (Page 12 Line 234-239)

4. Histopathology shows malignant nature of the disease, why radical cystectomy is not offered.

Response:

The reviewer's comments are well taken and appreciated. Despite the final histology showed the atypical type which may indicates malignant potency of the tumor, the management of the bladder GCT has not certainly clarified yet, and depending on the current consensus and optimistic prognosis in our case, we finally performed the partial cystectomy instead of radical cystectomy to reach better survival quality. Indeed, we will sustain the follow-up, and the radical surgery would be necessary if the recurrence or metastasis occurs. We have specified the manuscript as follows to make this clearer.

Despite this may indicates malignant potency of the tumor, depending on the current consensus and optimistic follow-up result in our case, we finally performed the partial cystectomy instead of radical cystectomy to reach better survival quality. (Page 11 Line 231- Page 12 Line 234)

Reviewer #5:

Maybe you can add some additional information regarding patient evaluation and possible connection with anomaly (kidney genesis and uterus didelphys)

Response:

We really appreciate the reviewer's suggestion. Unilateral renal anomaly (RA) accounts for 5 percent of the renal malformations. Although the patients usually present no symptoms, unilateral RA can be accompanied by other ectopic kidney, nonrenal anomalies and evidence of renal injury, such as contralateral renal hypertrophy, Branchio-renal syndrome (commonly associated with hearing abnormality), renal malfunctions and Müllerian defects (eg, uterine didelphys and/or vaginal duplication) which are common in girls with RA. Moreover, we've already

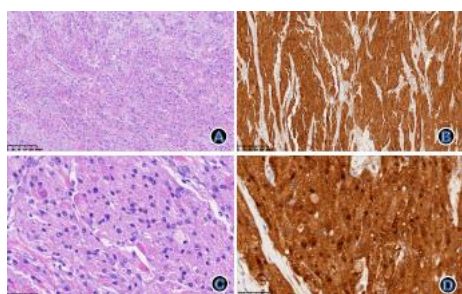
specified the corresponding information about patient evaluation and anomalies on manuscript as follows.

Significantly, the patient previously had left kidney agenesis and diabetes mellitus. Unilateral renal agenesis patients usually accompanied by other ectopic kidney, nonrenal anomalies and evidence of renal injury, such as contralateral renal hypertrophy, Branchio-o-renal syndrome (commonly associated with hearing abnormality), renal malfunctions and Müllerian defects (eg, uterine didelphys and/or vaginal duplication) which are common in girls. Unfortunately, depending on the illustrations of current reports, there is no relations between GCT and unilateral renal agenesis. In our case, the patient had a normal contralateral kidney size, which was not accompanied with hearing abnormality, renal injury (eg, hypertension or proteinuria), abnormal serum creatinine and GFR, however, the uterine didelphys present. And we will continue perform the urinalysis of this patient during every follow-up to monitor the renal function of the contralateral kidney. (Page 12 Line 242-253)

Reviewer #6:

1. Please provide high power fields of histological findings in addition to others immunohistochemical pictures.

Response: Thanks for the reviewer's comments and suggestions. As recommended, we've already added high power fields of histological findings (Page 17).



2. The authors should include in the discussion the differential diagnosis with other tumors with granular cell changes, for instance, leiomyosarcoma with granular cell, angiosarcomas with granular cell, melanoma etc.

Response:

Thanks for the reviewer's constructive suggestion. The differential diagnosis have been enriched on the sentence of our manuscript.

GCT is mainly derived from Schwann cells and consists of large polymorphic cells containing a large amount of granular cytoplasm, and it is usually difficult to distinguish GCT from other neurogenic tumors only depending on the perspective of cellular morphology and radiology. For instance, Schwannoma is completed

composed of differentiated neoplastic Schwann cells (Fletcher CDM *et al.*, 2013) and ganglioneuroma is mainly composed of mature Schwannian stroma and mature ganglion cell (Shimada H *et al.*, 1999)^[6-8]. (Page 9 Line 178-185)

It should be noticed that malignant GCT tends to be misdiagnosed as melanoma due to positive IHC staining of S-100 and SOX10 in both cancers. However, HMB45 staining is positive in melanoma and negative in GCT(Sun Yue *et al.*, 2018)^[2, 9]. (Page 10 Line 195-198)

3.CD56 and SOX10 immunoreactivity is missing? CD68, inhibin, calretinin immunostain are missing.

Response:

The reviewer's comment is well taken. Although there are several immunohistochemical markers, the S-100 and pancytokeratin are the most specific and common biomarkers regarding to all of the former cases especially the recent report from Sun Yue *et al.*, so we presumed that other immunoreactivity such as CD56, SOX10 etc. may not be further tested under the condition of current pathological diagnosis. Of course, we would like to run additional test on more positive protein of the GCT if necessary.

Reviewer #7:

1.Why did the woman undergo an ultrasound scan?

Response:

1. Thanks for the reviewer's valuable suggestions. The ultrasound scan was one of the annual physical examination items at local community.

2.“Blood, urine and stool cultures for ova and parasites showed negative results.” This statement should be modified. Blood and urine are cultured for bacteria and fungi not for ova and parasites. It should be microscopy of the urine and stool.

Response:

Thanks for the reviewer's critic suggestion. Inspired by the reviewer, we have modified the grammar mistakes and specified the contents on the manuscript as follows.

Blood, urine and stool routine were within the normal range, and microscopy for bacteria and fungi showed negative results. (Page 6 Line 115-116)

3.Why were the cultures performed as the first investigation?

Response:

We're sorry to mistaken the term “blood, urine and stool culture” to “ blood , urine and stool routine” at the first investigation, and we have corrected the mistake on our

manuscript.

Blood, urine and stool routine were within the normal range, and microscopy for bacteria and fungi showed negative results. (Page 6 Line 115-116)

4. Why were random tumor markers performed like CA 19.9, CA 125, AFP for urinary bladder lesion in the absence of any other evidence. Ca 199 is written wrong.

Response:

The reviewer's comment is well taken. CA199, CA125, AFP etc. were used for routine screening for metastatic tumor from other primary organs like gastrointestinal tract, ovary, liver and so on. We have enriched the content on the original paper.

Tumor markers such as CA199, CA125, CEA and AFP which were used for routine screening for metastatic tumor from other primary organs like gastrointestinal tract, ovary, liver ...were not remarkable. (Page 6 Line 119-121).

5. "semispherical neoplasm" should be written as semispherical shaped lesion.

Response:

We appreciate the reviewer's correction. We've already replaced all the "semispherical neoplasm" term as "semispherical shaped lesion" which been red-marked in the manuscript as the following sentence.

- Cystoscopy revealed a semispherical shaped lesion measuring (Page 3 Line 54)
- Cystoscopy revealed a semispherical shaped lesion measuring about 4.0 cm in diameter (Page 6 Line 124)
- **Pre-operative cystoscopy examination:** A semispherical shaped lesion, measuring about 4.0 cm in diameter (Page 16 Line 374)

6. "left and top wall"- it is roof not top wall.

Response:

We appreciate the reviewer's correction. We've already replaced all the "left and top wall" term as "left wall and roof" which been marked with red line in the manuscript.

- measuring about 4.0 cm in diameter at the junction of the left wall and roof of bladder (Page 3 Line 55)
- at the junction of the left wall and roof of bladder (Page 6 Line 125)
- at the junction of the left wall and roof and covered with normal bladder mucosa. (Page 16 Line 375)

7.Expand the abbreviation - CT scan, MRI, IHC, NSE, DFS, PET-CT

Response:

Thanks for the reviewer's correction. The abbreviation of CT scan, MRI, and IHC and so on were expanded and red-marked in the manuscript as follows.

- **Computed tomography (CT)** scan demonstrated a high density lesion .(Page 3 Line 56)
- Contrast-enhanced pelvic **magnetic resonance imaging (MRI)** revealed a space-occupying lesion (SOL) . (Page 3 Line 56)
- depending on radiologic and pathological findings without **immunohistochemical (IHC) staining**. (Page 5 Line 94)
- positive **neuron-specific enolase (NSE)**, and weak positivity of both Ki-67 (5%) and CD-68. (Page 8 Line 149)
- Partial cystectomy is the treatment of choice to minimize recurrence and improve **disease-free survival (DFS)** in benign cases. (Page 4 Line 80)
- The patient underwent **positron emission tomography-computed tomography (PET-CT)** (18F-FDG) three weeks after operation. (Page 8 Line 157)

8.“soft tissue shadow” , “CT value” – This is not the terminology used in CT scan reporting

Response:

Thanks for the reviewer's suggestion. The term “soft tissue shadow” was corrected to “high density lesion”, and the term “CT value” was corrected to “CT number” and all the replacement were red-marked as follows.

- demonstrated a **high density lesion** on the left wall. (Page 3 Line 57)
- revealed a **high density lesion** on the left wall of the bladder (Page 7 Line 127)
- The white arrow indicated that a **high density lesion** is seen (Page 16 Line 381)
- with a mean **CT number** of 44HU. (Page 7 Line 128)
- with clear boundaries, with a mean **CT number** of 44HU. (Page 16 Line 382)

9.non-mucosal origin/external pressure- Means?

Response:

The reviewer's comment is valuable. As for “non-mucosal origin/external pressure” of the MRI reports, we apologize for that we didn't describe it clearly. The words means the lesion didn't originate from urothelium of bladder wall but it tends to

proliferate externally into the cavity of urinary bladder. It have been revised on the manuscript.

Contrast-enhanced MRI revealed a space-occupying lesion (SOL) on the left wall of the bladder, the SOL didn't originate from urothelium of bladder wall but it tends to generate externally into the bladder cavity. (Figure 3) (Page 7 Line 129-131)

10.Final diagnosis to be mentioned after treatment.

Response:

Thanks for the reviewer's constructive suggestion. We've already move the "Final Diagnosis" part after the "Management" to make sure the article looks more logic.(Page 8 Line 152-154).

11.Why was PET-CT performed and what was done as report showed PET avid retroperitoneal lymph nodes. What was the cause.

Response:

We are deeply thankful to the reviewer for raising this important point. Because of the rare atypical GCT diagnosis as well as the uncertain prognosis currently, we performed the PET-CT for metastatic tumor screening from other original organs. Although the lymph nodes enlargement was detected by PET-CT three weeks after surgery, the following routine CT Scan performed every three months during follow-up revealed that there is no recurrence or apparent lymph node enlargement of retroperitoneal and bilateral iliac vascular region. In view of the above, we attribute the disparity reports about lymph nodes on PET Scan and Ct scan to the irritable inflammatory reaction, and we have specified this description on the manuscript as follows.

Furthermore, the lymph nodes enlargement of retroperitoneal and bilateral iliac vascular region was detected by PET Scan three weeks after operation, nevertheless, the following routine CT Scan during follow-up revealed that there is no recurrence or apparent lymph node enlargement. In view of the above, we attribute the disparity reports about lymph nodes on PET Scan and Ct scan to the irritable inflammatory reaction. (Page12 Line 234-239)

12.Conclusion should be shortened.

Response:

Thanks for the reviewer's comment. We've already simplified a part of "Conclusion" on manuscript.

Bladder GCT is not common and malignant GCT is extremely rare. IHC characteristics such as S-100, SOX10, CD56, HBM45 and pancytokeratin are essential for the diagnosis. In addition, ATP6AP1, ATP6AP2, BRD7 and GFRA2 gene mutations cannot be neglected in terms of further diagnosis and targeting therapy. (Page 13 Line 256-259)

Science editor:

1.The title is too long, and it should be no more than 18 words;

Response:

Thanks for the reviewer's suggestion. We've already simplified the title in the manuscript:

Atypical granular cell tumor of the urinary bladder: a case report and literature review (Page 1 Line 4-5)

2.The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response:

The reviewer's comment is valuable. We've already prepared the original figures using PowerPoint format as recommended and we will also upload them as the request of guideline.

Once again, we appreciate the opportunity to make these revisions to our manuscript, and are grateful for the constructive suggestions and support of Editor and Reviewers. We have tried to address the issues to the best of our ability and hope that our revisions meet the requirements of our conditional acceptance, ultimately enabling our manuscript to be published in the *World Journal of Clinical Cases*.

Sincerely,

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